IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Masatoshi CHIBA

Group Art Unit: 1649

Serial No : 09/926,661

Examiner: Daniel E. Kolker

Filed : February 28, 2002

For : LYOPHILIZED HGF PREPARATIONS

REQUEST FOR PRE-APPEAL BRIEF REVIEW

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Window, Mail Stop **AF**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This request is being filed concurrently with a Notice of Appeal and is responsive to the Final Official Action of February 16, 2006. Submitted herewith is a Request for Two-Month Extension of Time to extend the period for response two months, from May 16, 2006, to July 17, 2006 (July 16, 2006 falling on a Sunday).

The undersigned authorizes the charging of any additional fees, including any extensions of time fees required to place the application in condition for allowance by Examiner's Amendment, to Deposit Account No. 19 - 0089 in order to maintain pendency of this application.

Reconsideration and withdrawal of the 35 U.S.C. §§ 102 and 103 rejections is respectfully requested in view of the following remarks.

The Office Action asserts Nakamura et al. (EP 0 456 188 A1) discloses the invention as claimed in claims 1, 3, 4, 6-9, and 12-15.

Applicant submits that Nakamura et al. does not specifically teach every element of Applicant's claimed invention. Applicant notes that for anticipation to exist, Nakamura et al. must clearly and unequivocally disclose the claimed invention without any need for picking, choosing, or combining various disclosures.

The final Office Action states that Applicant's stabilizer, arginine, is disclosed in Nakamura et al., referring to column 9, lines 52-58. The cited passage is set forth in its entirety, as follows:

> The therapeutic agents for hepatocirrhosis of the invention *may* contain other additives such as stabilizers, excipients, dissolution-promoters, adsorption-preventors and antioxidants, and examples thereof include, for example, sugars such as mannitol and glucose, amino acids such as glycine, alanine, lysine and arginine, proteins such as albumin, alcohols such as ethylene glycol and glycerol, hydrophilic polymers such as polyethylene glycol, inorganic salts such as NaCl, organic salts such as sodium citrate, surfactants such as Polysorbate 80 and reducing agents containing sulfur, which may be used alone or in combination.

(EP 0 456 188 A1, column 9, line 52 – column 10, line 6, emphasis added.) The final Office Action refers to the previous Office Action for a description of the other elements of the rejection.

In the previous Office Action (mailed August 18, 2005), the Action states that "Nakamura teaches a lyophilized preparation comprising the following components: 1 mg HGF, 100 ml of phosphate buffer, 0.15 M NaCl (see column 14, lines 25-35)." (Office Action mailed August 18, 2005, page 4, lines 5-7.) The Office Action cites to column 9, line 52 – column 10, line 13 for the disclosure of stabilizing agents. The Office Action thus concludes that "[t]he preparation [of Nakamura] contained 0.01 mg/ml of HGF, and is to be reconstituted at 0.01 mg/ml." (Office Action mailed August 18, 2005, page 4, lines 8-9.) The passage at column 14, lines 25-35 is reproduced as follows:

> Example 1
> An aqueous solution is prepared aseptically by adding 1 mg of a hepatocyte growth factor and 100 mg of human serum albumin to 100 ml of 0.02 M phosphate buffer (pH 7.4) containing 0.15 M NaCl and 0.01% Polysorbate 80, and filled in a vial at 1 ml per vial, followed by lyophilization and sealing. Injectable distilled water is filled in an ampoule at 1 ml each for dissolution.

(EP 0 456 188 A1, column 14, lines 25-35.)

In addressing the Office Actions' points, Applicant notes that Nakamura et al. is relied upon by the Office for particular elements of Applicant's claims: 1 mg HGF, 100 ml of phosphate buffer, 0.15 M NaCl, and the Office Action specifically refers to column 14, lines 25-35 for that particular disclosure. It is factually incorrect to state that Nakamura teaches a lyophilized preparation "comprising" those components. (Office Action mailed August 18, 2005, page 4, lines 5-7.) That disclosure is very specific, and states exactly what is included, described in precise amounts and concentrations.

Applicant also respectfully disagrees with the statements that arginine is described in Nakamura et al. as a stabilizing agent. Arginine, along with glycine, alanine, and lysine, are described as "amino acids," but are not characterized by Nakamura et al. as being anything other than "additives." Nakamura et al. describes additives as including stabilizers,

excipients, dissolution-promoters, adsorption-preventors, and antioxidants. Nakamura et al. further discloses "examples" of additives as including, for example, sugars, amino acids, proteins, alcohols, hydrophilic polymers, inorganic salts, organic salts, surfactants, and reducing agents. However, Nakamura et al. does not state how the examples correlate with the subclasses of additives that are listed. Thus, while Applicant's specification states that arginine, as well as other amino acids, can be used as stabilizers, that information is not provided by Nakamura et al., and to suggest that Nakamura et al. discloses arginine – or any other particular amino acid – for use as a stabilizer, is incorrect.

Applicant submits that Nakamura et al. does not anticipate the present invention and that the final Office Action has picked and chosen from its disclosure in order to arrive at all of the claimed elements. Applicant notes that Example 1 from Nakamura et al. (column 14, lines 25-35) contains, in addition to the HGF, phosphate buffer, and NaCl identified by the final Office Action, human serum albumin and Polysorbate 80. It does not contain arginine.

Applicant notes that both albumin and Polysorbate 80 are identified in Nakamura et al. as being "additives" that may be contained in the therapeutic agents of Nakamura et al. (Column 9, lines 58 – column 10, line 1 (albumin); column 10, lines 4-5 (Polysorbate 80)). Thus, Nakamura et al. specifically chose certain "additives" – human serum albumin and Polysorbate 80 – but it specifically excluded others. To state that Nakamura et al. discloses a composition having 1 mg HGF, 100 ml of phosphate buffer, 0.15 M NaCl, *and* arginine, is incorrect.

The Office is not free to pick and choose from disclosures to arrive at a claimed invention, so as to defeat patentability. The statutes and case law very clearly require a specific disclosure of each element of a claimed invention – all in one place – for anticipation to stand. Nakamura et al. does not provide such disclosure.

The Office Action asserts Nakamura et al. anticipates or renders obvious claims 1 and 16.

Applicant notes that while the Office Action states that these claims are anticipated by, or in the alternative, obvious over Nakamura et al., the Office Action fails to make any case for the obviousness of these claims. The Office Action fails to address any of the three requirements of a *prima facie* case of obviousness: motivation, expectation of success, and presence of all claimed elements. For this technical deficiency alone, the rejection should be withdrawn.

Applicant additionally notes that a *prima facie* case cannot be made from Nakamura et al. for at least the following reasons. As noted above, the specific compositions disclosed

by Nakamura et al. do not include arginine. Moreover, there is nothing in Nakamura et al. that would cause one of ordinary skill in the art to add arginine, or to replace another component of Nakamura et al.'s compositions, with arginine. There is no suggestion of its desirability as an additional additive, and thus, there is no reason one of skill in the art would add it to Nakamura et al.'s compositions. Additionally, there is no suggestion of its interchangeability with some other component already present in one of Nakamura et al.'s compositions. For these reasons, there is no reason that a person of skill in the art would select, from all of the choices of "additives" in Nakamura et al., arginine.

Additionally, there is not a reasonable expectation of success in a modification of Nakamura et al. that would result in the presently claimed invention. Applicant refers the Office to the "Background Art" section of the present specification, which describes at least two published HGF formulations, examples of which are described as including, for example, human serum albumin, mannitol, lysine, arginine, glycine, and alanine, as stabilizing agents. However, each of these formulations is described as being unacceptable: one for lack of long-term stability, and the other for being undesirable for human administration. Applicant submits that modifying or changing the additives in HGF formulations can result in unexpected results and undesirable final products. Without more, there is no reasonable expectation of success in a modification of Nakamura et al.

The Office Action rejects claims 1, 3, 4, and 6-16 under 35 U.S.C. § 103(a) as allegedly unpatentable over Nakamura et al. in view of Tanaka et al. (WO 97/02832).

Applicant has noted above the reasons why Nakamura et al. does not anticipate or render obvious the presently claimed invention. Still further, Applicant respectfully submits that Tanaka et al. fails to supply Nakamura et al.'s missing teachings and also fails to provide motivation to make any change to Nakamura et al. to arrive at the presently claimed invention.

Still further, the Office admits that Nakamura et al. does not disclose Applicant's specifically claimed pH range (see claim 10, for example), but relies upon Tanaka et al. for this missing teaching. However, Applicant respectfully submits that a *prima facie* case of obviousness does not result.

Initially, Applicant notes that there is nothing in Nakamura et al. that would lead to the selection of a different pH than that disclosed, i.e., pH 7.4. While it is not explicitly stated, it is reasonable to conclude that the choice of pH 7.4 was made to closely match physiological pH. However, there is nothing in Nakamura et al. that would suggest that such pH is

undesirable. Thus, there is no reason to turn to the disclosure of Tanaka et al. for the choice of a different pH.

Additionally, if anything, Tanaka et al. teaches away from the present invention, which requires a concentration of less than 5 mg/ml. Tanaka et al. specifically states that the solubility of TGF varies with pH and that the solubility is 0.1 to 5 mg/ml at pH 7, but the solubility is over 20 mg/ml at pH 5. (Tanaka et al., paragraph [0018]). Tanaka et al. then proceeds to state that therefore, "it is *preferred* to keep the pH around 5.0 to 6.0." (Id., emphasis added.) Thus, Tanaka et al. clearly suggests a higher concentration of HGF than 5 mg/ml.

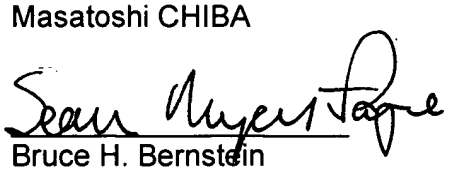
Applicant respectfully submits that a *prima facie* case of obviousness does not result from the combination of Nakamura et al. and Tanaka et al. and respectfully requests withdrawal of the rejection for obviousness.

CONCLUSION

Reconsideration of the Final Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
Masatoshi CHIBA



Bruce H. Bernstein
Reg. No. 29,027 42,920

July 17, 2006
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191